

PROCESS FOR PREPARING 3-HETEROARYL-3-HYDROXYPROPANOIC ACID DERIVATIVES

5

BACKGROUND OF THE INVENTION

Field of the Invention: The invention relates to a process for preparing enantiomer-enriched 3-heteroaryl-3-hydroxypropanoic acid derivatives and 3-heteroaryl-1-aminopropan-3-ols, and to their use.

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Brief Description of the Prior Art: 3-Heteroaryl-3-hydroxypropanoic acid derivatives and 3-heteroaryl-1-aminopropan-3-ols have gained industrial significance, in particular, as intermediates for producing medicaments. Illustratively, some 3-heteroaryl-3-hydroxypropanoic acid derivatives and 3-heteroaryl-1-aminopropan-3-ols are used as precursor substances for preparing inhibitors of the uptake of serotonin or noradrenaline. In the case of some of these inhibitors, it has been shown that certain enantiomers are not only inactive, or less active, but are even able to exhibit undesirable side-effects (US-A 5 104 899).

The art-known processes for preparing these enantiomers and the attendant disadvantages are as follows. A process for preparing enantiomer-enriched (1S)-3-(methylamino)-1-(2-thiophenyl)-1-propanol proceeding from 1-(2-thiophenyl)-3-chloropropan-1-one is described in Chirality 2000, 12, 26-29. Following reduction to the racemic 3-chloro-1-(2-thienyl)-1-propanol, the racemate is resolved enzymically and the (S) enantiomer is subjected to further reaction with Nal and methylamine to give (S)-3-(methylamino)-1-(2-thiophenyl)propan-1-ol. This method suffers from the disadvantage that, in principle, only 50% of the desired enantiomer can be obtained when racemates are resolved enzymically and the total yield is therefore economically unacceptable.

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It is known that microorganisms, such as yeasts or fungi, can be used to reduce 3-oxocarboxylic acid derivatives enantioselectively to give the corresponding enantiomer-enriched 3-hydroxycarboxylic acid derivatives (see also Sybesma et al., *Biocatalysis and Biotransformation*, 1998, Vol. 16, 95-134; Dahl et al., *Tetrahedron: Asymmetry* 10, 1999, 551-559, Dehli et al., *Tetrahedron: Asymmetry* 11, 2000, 3693-3700, Hayakawa et al., *Tetrahedron Letters*, 1998, Vol. 39, 67-70, Cabon et al., *Tetrahedron: Asymmetry* 6, 1995, 2199-2210 and Smallridge et al., *Tetrahedron Letters*, 1998, Vol. 39, 5121-5124).

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In addition, EP-A 447 938 describes the enantioselective synthesis of 2-halo-3-hydroxy-3-phenylpropanoic esters by using various organisms to reduce the 2-halo-3-oxo-3-phenylpropanoic esters.

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Furthermore, Chenevert et al., *Tetrahedron* 1992, Vol.48, 6769-6776 disclose the asymmetric synthesis of both enantiomers of the antidepressant fluoxetine (N-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine hydrochloride). An important step in the multi-stage synthesis is that of using microorganisms to effect the enantioselective reduction of the ethyl 3-oxo-3-phenylpropanoate.

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An analogous synthesis, for preparing (R)-tomoxetine, which acts as an antidepressant, is described in Kumar A. et al., *Tetrahedron Letters*, 1991, Vol. 32, 1901-1904. Reportedly, the enantioselective reduction of the ethyl 3-oxo-3-phenylpropanoate to give ethyl 3-hydroxy-3-phenylpropanoate is an important step in this synthesis as well.

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However, the enantioselective reduction of heteroaryl ketones has not previously been described.

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There was still the need to provide a process which makes it possible to prepare enantiomer-enriched 3-heteroaryl-3-hydroxypropanoic acid derivatives.

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SUMMARY OF THE INVENTION

In accordance with the foregoing, a process for preparing stereoisomer-enriched 3-heteroaryl-3-hydroxypropanoic acid derivatives has now been found, which process is characterized in that compounds of the formula (I)



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in which

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heteroaryl is a monocyclic or bicyclic aromatic radical having a total of from 5 to 10 ring atoms, where none, one or two ring atoms, selected from the group oxygen, sulphur and nitrogen, can be present per cycle and one or two can be present in the entire aromatic radical, and where the monocyclic or bicyclic aromatic radical is optionally substituted, once, twice or three times, by radicals which are selected, in each case independently of each other, from the group hydroxyl, C₁-C₈-alkyl, cyano, COOH, COOM, where M is an alkali metal ion or a half equivalent of an alkaline earth metal ion, COO-(C₁-C₄-alkyl), O-(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, NH-(C₁-C₄-alkyl), fluorine, NO₂, chlorine, bromine, C₁-C₄-fluoroalkyl, CONH₂ or CONH-(C₁-C₄-alkyl), and

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W is C(O)YR¹_n, where Y is = oxygen and n is = 1, or Y is nitrogen and n is = 2, or

W is CN, and

R¹ are, in each case independently of each other, hydrogen, C₁-C₈-alkyl, C₄-C₁₀-aryl or C₅-C₁₁-arylalkyl or, when Y is nitrogen, the two radicals R¹ are together C₃-C₅ alkylene,

5 are reacted in the presence of microorganisms and/or cell preparations thereof, and

in the presence of water having a pH range of from 3 to 11, based on 25°C,

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and, in this way, enantiomer-enriched compounds of the formula (II),



15 in which heteroaryl and W have the abovementioned meaning, are obtained.

Within the context of the invention, all the radical definitions, parameters and specifications which are mentioned in general or which are mentioned
20 in preference, as stated above or below, can be combined amongst themselves, that is between the respective ranges and preference ranges as well, in any arbitrary manner.

Within the meaning of the invention, the term enantiomer-enriched
25 encompasses, in particular, enantiomerically pure compounds or arbitrary mixtures of enantiomers in which one enantiomer is present in a larger proportion than the other enantiomer, preferably in a relative proportion of from 60% to 100 mol%, particularly preferably from 80 to 100 mol% and, very particularly preferably, from 90 to 100 mol%.

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DETAILED DESCRIPTION OF THE INVENTION

Within the context of the invention, **alkyl** is, in each case independently, a straight-chain or cyclic, independently thereof branched or unbranched, alkyl radical which can be further substituted by C₁-C₄-alkoxy radicals. The
5 same applies to the nonaromatic moiety of an arylalkyl radical.

For example, within the context of the invention, C₁-C₄-alkyl is methyl, ethyl, 2-ethoxyethyl, n-propyl, isopropyl, n-butyl and tert-butyl, while C₁-C₈-alkyl is, in addition to this, for example, n-pentyl, cyclohexyl, n-hexyl, n-
10 heptyl, n-octyl or iso-octyl.

Fluoroalkyl is, in each case independently, a straight-chain, cyclic, branched or unbranched alkyl radical which is substituted, once, more than once or completely, by fluorine atoms.

15 For example, C₁-C₄-fluoroalkyl is trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, nonafluorobutyl and heptafluoroisopropyl.

Within the context of the invention, **aryl** is, for example and preferably, carbocyclic aromatic radicals or heteroaromatic radicals which contain no,
20 one or two, but at least one in the entire heteroaromatic radical, heteroatom(s) which is/are selected from the group nitrogen, sulphur and oxygen.

In addition, the carbocyclic aromatic radicals or heteroaromatic radicals
25 can be substituted by one or two substituents per cycle, which substituents are selected, in each case independently of each other, for example and preferably, from the group hydroxyl, C₁-C₄-alkyl, cyano, COOH, COOM, where M is an alkali metal ion or a half equivalent of an alkaline earth metal ion, COO-(C₁-C₄-alkyl), O-(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, NH-(C₁-C₄-alkyl), fluorine, chlorine, bromine, C₁-C₄-fluoroalkyl,
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CONH₂ or CONH-(C₁-C₄-alkyl). The same applies to the aryl moiety of an arylalkyl radical.

- In the formulae (I) and (II), heteroaryl is preferably a monocyclic aromatic radical having a total of 5 or 6 ring atoms in which one or two ring atoms are selected from the group oxygen, sulphur and nitrogen and where the monocyclic aromatic radical contains no, one or two radical(s) which is/are selected, in each case independently of each other, from the group methyl, ethyl, n-propyl, isopropyl, cyano, COOH, COONa, COOK, COO-methyl, COO-ethyl, COO-tert-butyl, COO-phenyl, methoxy, ethoxy, dimethylamino, diethylamino, methylamino, ethylamino, fluorine, chlorine, NO₂, trifluoromethyl, pentafluoroethyl, heptafluoroisopropyl, CONH₂ and CONH-methyl.
- Heteroaryl is, particularly preferably, 2- or 3-thiophenyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 3- or 4-pyrazolyl, 1-, 2- or 4-thiazolyl, 1-, 2- or 4-oxazolyl, 2-, 4- or 5-imidazolyl, 2-, 3- or 4-pyridyl, 2- or 3-pyrazinyl, 2-, 4- or 5-pyrimidyl, 3-, 4-, 5- or 6-pyridazinyl, 2- or 3-indolyl, 3-indazolyl, indazolyl, 2- or 3-benzo-furanyl, 2- or 3-benzothiophenyl, 2-, 3- or 4-quinolinyl or isoquinolinyl, where each of the radicals mentioned carries no, one or two, and preferably no, substituents which are in each case selected, independently of each other, from the group methyl, ethyl, n-propyl, isopropyl, cyano, methoxy, ethoxy, fluorine, chlorine, trifluoromethyl, pentafluoroethyl and heptafluoroisopropyl.

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Heteroaryl is very particularly preferably 2-thiophenyl.

R¹ is preferably CN or COOR¹, where R¹ is hydrogen or methyl or ethyl.

- Preferred compounds of the formula (I) are methyl 3-oxo-3-(2-thiophenyl)-propanoate, ethyl 3-oxo-3-(2-thiophenyl)propanoate, methyl 3-oxo-3-(3-

thiophenyl)propanoate, ethyl 3-oxo-3-(3-thiophenyl)propanoate, methyl 3-oxo-3-(2-furanyl)propanoate, ethyl 3-oxo-3-(2-furanyl)propanoate, methyl 3-oxo-3-(3-furanyl)propanoate, ethyl 3-oxo-3-(3-furanyl)propanoate, methyl 3-oxo-3-(2-pyridinyl)propanoate, ethyl 3-oxo-3-(2-pyridinyl)propanoate, methyl 3-oxo-3-(3-pyridinyl)propanoate, ethyl 3-oxo-3-(3-pyridinyl)propanoate, methyl 3-oxo-3-(4-pyridinyl)propanoate, ethyl 3-oxo-3-(4-pyridinyl)propanoate, 3-oxo-3-(2-thiophenyl)propanonitrile, 3-oxo-3-(3-thiophenyl)propanonitrile, 3-oxo-3-(2-furanyl)propanonitrile, 3-oxo-3-(3-furanyl)propanonitrile, 3-oxo-3-(2-pyridinyl)propanonitrile, 3-oxo-3-(3-pyridinyl)propanonitrile, 3-oxo-3-(4-pyridinyl)propanonitrile and N-(methyl)-3-oxo-3-(2-thiophenyl)propanamide.

The microorganisms which are preferably employed are bacteria, yeasts or fungi, with both wild types and transformed strains being included.

Microorganisms which are particularly preferred are yeasts and fungi, very particularly preferably those of the genera *Saccharomyces*, *Geotrichum*, *Candida*, *Pichia*, *Hansenula*, *Yarrowia*, *Rhizopus*, *Mortierella*, *Mucor*, *Sporotrichum*, *Rhodotorula*, *Trichoderma*, *Aspergillus*, *Penicillium*, *Pullaria*, *Cunninghamella* and *Curvularia*.

Microorganisms which are even more preferred are *Saccharomyces cerevisiae* and *Geotrichum candidum*.

Cell preparations are to be understood as meaning: purified or unpurified lysed cells which can be used either in the moist state or in the dried state, for example as lyophilisates.

Preference is given to using microorganisms.

In a preferred embodiment, the microorganisms are grown, prior to the compounds of the formula (I) being reacted, on complex or mineral nutrient media, using culturing methods which are customary per se for growing the given microorganisms, such as culturing in shaken flasks, batch fermentations, fed-batch fermentations or continuous fermentations, up to an optical density of from 1 to 800, preferably of from 5 to 300, measured at a wavelength of 600 nm (OD_{600}), and concentrated, where appropriate, after having been grown.

The microorganisms can be grown, for example, at temperatures of between 10 and 60°C, preferably of between 20 and 40°C.

The pH, when growing the microorganisms can, for example, be between pH 3 and pH 9, preferably between pH 4 and pH 8, particularly preferably between pH 5 and pH 7.5. In this connection, pH values are in each case based on 25°C, within the entire scope of the invention.

The microorganisms can be grown under aerobic or anaerobic conditions; they are preferably grown aerobically.

For the reaction, the compound of the formula (I) is, in a preferred embodiment, added to the microorganisms which are either present in the growth medium or resuspended, where appropriate after prior sedimentation, in an isotonic solution. In this connection, the isotonic solution can be a mineral salt solution or also a nutrient medium for microorganisms.

The mixture can, for example and preferably, be shaken or stirred and, where appropriate, aerated.

The process according to the invention can be carried out in a pH range of from pH 3 to pH 11, preferably of from pH 4 to pH 10, and particularly preferably of from pH 6 to pH 8.

- 5 The process according to the invention is, furthermore, customarily carried out at a temperature of from 10 to 60°C, preferably of from 18 to 45°C.

The duration of the reaction can be from 10 min to 96 hours, preferably from 60 min to 72 hours and particularly preferably from 2 to 48 hours.

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The process according to the invention can be carried out such that the compounds of the formula (I) are added once, several times or continuously.

- 15 The sum of the concentrations of the compounds of the formulae (I) and (II) in the cell suspension can be between 1 and 900 mM, preferably between 2 and 500 mM, particularly preferably between 3 and 250 mM.

- 20 In order to increase the solubility of the starting compound in the reaction medium, it is possible, in a preferred embodiment, to add auxiliary substances such as polar, water-miscible solvents, such as glycerol, dimethylformamide or dimethyl sulphoxide, or other auxiliary substances, such as cyclodextrins.

- 25 Also, the process according to the invention can be carried out in the presence of an organic solvent, for example in a multiphase system such as, in particular, a two-phase system.

- 30 Organic solvents which are suitable for this purpose are, for example, organic solvents which are not miscible with water or which are miscible with at most 10% by volume, such as aliphatic or aromatic, where

appropriate chlorinated, solvents, such as petroleum ether, hexane, octane, heptane, toluene, the isomeric xylenes, chlorobenzene, dichloromethane and silicone oils. Frequently, the starting compound can also itself be used as the organic phase.

5

The compounds of the formula (II) can be isolated in a manner known per se, for example by extracting with an organic solvent, or isolated, if a multiphase system was used, by means of separating off the organic phase and, where appropriate, further extraction and subsequent removal
10 of the organic solvent.

Preference is given to using, for this purpose, solvents such as toluene, ethyl acetate, dichloromethane, isobutyl ketone, cyclohexane and methylcyclohexane, preferably ethyl acetate. The extraction can in this
15 case be effected by either continuously or discontinuously supplying the extracting agent. In the simplest case, the purification is effected by extracting, while shaking, with the previously mentioned extracting agents.

If desired, a further purification can be effected by means of distillation or,
20 in the case of compounds of the formula (I) which are solid at room temperature, by means of recrystallization.

If the process according to the invention is carried out in a multiphase system, the product can also be isolated directly by subjecting the organic phase to fractional distillation.

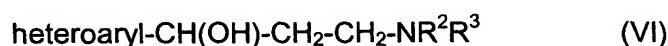
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In a manner according to the invention, the enantiomer-enriched compounds of the formula (II) are obtained, with the stereogenic carbon atom which carries the heteroaryl group and the hydroxyl group usually exhibiting the (S) configuration.

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The process according to the invention is particularly suitable for preparing methyl (S)-3-hydroxy-3-(2-thiophenyl)propanoate, ethyl (S)-3-hydroxy-3-(2-thiophenyl)propanoate, methyl (S)-3-hydroxy-3-(3-thiophenyl)propanoate, ethyl (S)-3-hydroxy-3-(3-thiophenyl)propanoate, methyl (S)-3-hydroxy-3-(2-furanyl)propanoate, ethyl (S)-3-hydroxy-3-(2-furanyl)propanoate, methyl (S)-3-hydroxy-3-(3-furanyl)propanoate, ethyl (S)-3-hydroxy-3-(3-furanyl)propanoate, methyl (S)-3-hydroxy-3-(2-pyridinyl)propanoate, ethyl (S)-3-hydroxy-3-(2-pyridinyl)propanoate, methyl (S)-3-hydroxy-3-(3-pyridinyl)propanoate, ethyl (S)-3-hydroxy-3-(3-pyridinyl)propanoate, methyl (S)-3-hydroxy-3-(4-pyridinyl)propanoate, ethyl (S)-3-hydroxy-3-(4-pyridinyl)propanoate, (S)-3-hydroxy-3-(2-thiophenyl)propanonitrile, (S)-3-hydroxy-3-(3-thiophenyl)propanonitrile, (S)-3-hydroxy-3-(2-furanyl)propanonitrile, (S)-3-hydroxy-3-(3-furanyl)propanonitrile, (S)-3-hydroxy-3-(2-pyridinyl)propanonitrile, (S)-3-hydroxy-3-(3-pyridinyl)propanonitrile, (S)-3-hydroxy-3-(4-pyridinyl)propanonitrile and N-(methyl)-(S)-3-hydroxy-3-(2-thiophenyl)propanamide.

The process according to the invention is furthermore suitable, in particular, as step a) in a process for preparing enantiomer-enriched compounds of the formula (VI),



in which

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heteroaryl has the same meaning as that given under formula (I), and

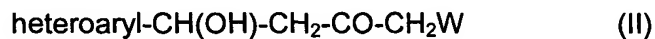
R^2 and R^3 are, in each case independently of each other, hydrogen, $\text{C}_1\text{-C}_8\text{-alkyl}$, $\text{C}_4\text{-C}_{14}\text{-aryl}$ or $\text{C}_5\text{-C}_{15}\text{-arylalkyl}$, or the two radicals R^2 and R^3 are together $\text{C}_3\text{-C}_{12}\text{-alkylene}$, which is characterized in that

30

in a step a),

compounds of the formula (I) are converted, as previously
described, into enantiomer-enriched compounds of formula (II)

5



where, in each case,

10

heteroaryl and W have the meanings mentioned under formula (I),
and

in a step b)

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i) when W is COOR¹ and R¹ is hydrogen, C₁-C₈-alkyl, C₄-C₁₀-
aryl or C₅-C₁₁-arylalkyl,

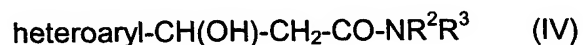
the enantiomer-enriched compounds of formula (II) are
reacted with amines of the formula (III)

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in which R² and R³ have the meaning mentioned under
formula (VI), to give enantiomer-enriched compounds of the
formula (IV)

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in which heteroaryl, R² and R³ have the previously mentioned
meanings, or

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- ii) when W is $\text{CON}(\text{R}^1)_2$ and the R^1 radicals are in each case, independently of each other, hydrogen, C_1 - C_8 -alkyl, C_4 - C_{10} -aryl or C_5 - C_{11} -arylalkyl, or the two R^1 radicals are together C_3 - C_5 -alkylene,

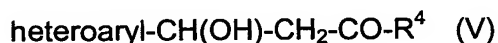
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the enantiomer-enriched compounds of the formula (II) are converted, where appropriate by reacting with amines of the formula (III), into enantiomer-enriched compounds of the formula (IV), and

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- iii) when W is CN, the compounds of the formula (II) are converted directly, by means of aminolysis/hydrolysis, into compounds of the formula (IV), or are initially converted, by means of hydrolysis, partial hydrolysis or mixed alcoholysis/hydrolysis, into compounds of the formula (V)

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in which heteroaryl has the meaning given under formula (I)

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and R^4 is OR^1 or NH_2 , where R^1 has the abovementioned meaning, and

are then converted, by amidation in analogy with i) or, where appropriate, in analogy with ii), into enantiomer-enriched compounds of the formula (IV)

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in a step c),

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the enantiomer-enriched compounds of the formula (IV) are converted, by means of reduction, into enantiomer-enriched

compounds of the formula (VI) having the abovementioned meaning.

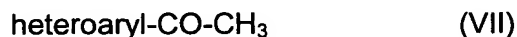
5 In the formulae (III), (IV) and (VI), R^2 and R^3 are particularly preferably, in each case independently, hydrogen, methyl, ethyl, isopropyl, phenyl or benzyl.

10 In the formulae (III), (IV) and (VI), NR^1R^2 is, in its entirety, particularly preferably methylamino, ethylamino and isopropylamino.

In the formulae (III), (IV) and (VI), NR^1R^2 is, in its entirety, very particularly preferably methylamino.

15 The compounds of the formula (I) which can be used for the process according to the invention comprising steps a), b) and c) are either known from the literature or can be prepared in analogy with the literature.

20 Compounds of the formula (I) in which W is not CN are preferably obtained by reacting compounds of formula (VII)



25 in which heteroaryl has the meaning and preference ranges mentioned under formula (I),

with compounds of the formula (VIII),



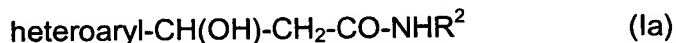
30 in which

R¹ and W have the same meanings as those which were given under the formula (I), with W not being CN, in the presence of a base.

5 The reaction of 2-acetylthiophene with dimethyl carbonate, diethyl carbonate, diphenyl carbonate or dibenzyl carbonate, methyl N-methyl carbamate, ethyl N-methyl carbamate, methyl N,N-dimethyl carbamate or ethyl N,N-dimethyl carbamate may be mentioned by way of example.

10 Such a reaction is described, for example, in Tetrahedron Lett. 1998, 39, 4995 and can be applied in an analogous manner, for example, for the reaction of 2-acetylthiophene with methyl N-methyl carbamate or ethyl N-methyl carbamate to give N-(methyl)-3-oxo-3-(2-thiophenyl)propanamide. It is furthermore also possible to obtain compounds of the formula (Ia)

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by reacting compounds of the formula (VII) with compounds of the formula (IX)

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in the presence of a base.

25 In step b) of the process according to the invention, the enantiomer-enriched compounds of the formula (II) are converted in a manner known per se, in accordance with i), ii) or iii), into enantiomer-enriched compounds of the formula (IV).

30 Illustratively, Houben Weyl "Methoden der Organischen Chemie [Methods of organic chemistry]", 4th edition, volume E 5, 941-1010 provides a

review of the preparation of carboxamides from carboxylic acids, carboxylic esters or other carboxamides.

If liquid or gaseous amines of the formula (III) are employed at room
5 temperature, preference is then given to using solutions of the amines. For example, in the case of methylamine, it is possible to advantageously use solutions consisting of methylamine in water, methanol or ethanol for reacting compounds of the formula (II) in which W is COOR¹. Reactions of amines of the formula (III) in the presence of coupling reagents such as
10 2-halopyridinium or 2-halo-1,3-thiazolium salts, or in the presence of acid cation exchangers, are suitable, for example, for converting free carboxylic acids of the formula (II) into the amides of the formula (IV).

According to step b), enantiomer-enriched compounds of the formula (IV)
15 are then obtained from enantiomer-enriched compounds of the formula (II).

The compounds of the formula (IV) can then be reduced to give the compounds of the formula (VI). The reduction of carboxamides to give the
20 corresponding amines is known in principle and is presented in summary in Houben Weyl "Methoden der Organischen Chemie", 4th edition, volume E 16 d, 987–1003.

Preference is given to reacting compounds of the formula (VI) with
25 complex boron hydrides or aluminium hydrides, such as lithium aluminium hydride, Red-Al® (sodium bis(2-methoxyethoxy)dihydroaluminate) or sodium borohydride.

Particular preference is given to reacting compounds of the formula (VI)
30 with lithium aluminium hydride.

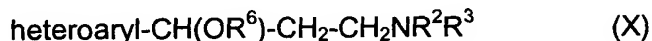
The reductions are preferably carried out at temperatures in the range from room temperature to 150°C, particularly preferably in the range from 50 to 110°C. While the reductions are usually carried out in ethers as solvents, preferably in cyclic ethers such as tetrahydrofuran or dioxane,
 5 reactions using Red-Al® can also be carried out in toluene as the solvent.

The enantiomer-enriched compounds of the formula (VI) are obtained in a manner according to the invention.

10 The following may be mentioned as being preferred compounds of the formula (VI):

(1S)-3-(methylamino)-1-(2-thiophenyl)-1-propanol, (1R)-3-(methylamino)-1-(2-thiophenyl)-1-propanol, (1S)-3-(dimethylamino)-1-(2-thiophenyl)-1-propanol and (1R)-3-(dimethylamino)-1-(2-thiophenyl)-1-propanol, with
 15 (1S)-3-(methylamino)-1-(2-thiophenyl)-1-propanol being even more preferred.

The enantiomer-enriched compounds of the formula (VI) which can be
 20 prepared in accordance with the invention are particularly suitable for preparing enantiomer-enriched compounds of the formula (X)



25 in which

heteroaryl, R² and R³ have the meanings and preference regions given under formula (I), and

30 R⁶ is phenyl or naphthyl which can be substituted, not at all, once or more than once, by substituents which are selected, in each case

independently of each other, from the group cyano, CO-(C₁-C₁₂-alkyl), O-(C₁-C₁₂-alkyl), (C₁-C₁₂-alkyl), fluorine, chlorine, bromine or C₁-C₁₂-fluoroalkyl.

R⁶ is preferably naphthyl.

5

Preferred compounds of the formula (X) are

(S)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine and (R)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine and their ammonium salts.

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The invention therefore also further comprises a process which

as step d),

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encompasses the reaction of enantiomer-enriched compounds of the formula (VI) with compounds of the formula (XI) to give enantiomer-enriched compounds of the formula (X) in the presence of a base.

20 In formula (XI),



R⁶ has the meaning mentioned under the formula (X), and

25

Hal is fluorine, chlorine, bromine or iodine, preferably fluorine.

1-Fluoronaphthalene and 4-chlorobenzotrifluoride are preferably used as compounds of the formula (XI).

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The bases which can be used are those which are able to at least partially deprotonate the compounds of the formula (VI) at the alcohol function.

- These bases include, for example, alkaline earth metal or alkali metal
- 5 hydrides, hydroxides, amides, alcoholates or carbonates, such as sodium hydride, sodium amide, lithium diethylamide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydroxide and potassium hydroxide.
- 10 The compounds which can be prepared in accordance with the invention are particularly suitable for use as active compounds in medicaments such as, in particular, inhibitors of serotonin or noradrenaline uptake, or as intermediates thereof.
- 15 The process according to the invention enjoys the advantage that it is possible to use readily available starting compounds to synthesize enantiomer-enriched 3-heteroaryl-3-hydroxypropanoic acid derivatives and 3-heteroaryl-1-aminopropan-3-ols, and their secondary products, on an industrial scale in high overall yields, high enantiomer excesses and high
- 20 purities.

The invention is further described by the following illustrative but non-limiting examples.

EXAMPLESExamples 1 and 2:

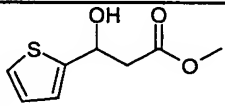
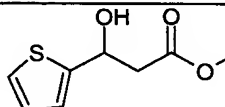
Reduction of methyl 3-oxo-(2-thiophenyl)propanoate using different strains of the baker's yeast *Saccharomyces cerevisiae*.

The yeast strains (*Saccharomyces cerevisiae* NG 247, Uniferm GmbH & Co KG, Monheim; *Saccharomyces cerevisiae* Y278, Deutsche Hefe Werke [German Yeast Works] GmbH & Co oHG, Hamburg) were grown overnight, at 28°C and with shaking (200 rpm), in 100 ml Erlenmeyer flasks containing 25 ml of YM medium (yeast extract, 3.0 g/l; malt extract, 3.0 g/l; peptone, 5.0 g/l; glucose, 10.0 g/l).

Each of the two yeast strains was incubated, at 28°C and while shaking (200 rpm), in three 1-litre Erlenmeyer flasks which contained 200 ml of YM medium which had previously been inoculated with 12 ml of preliminary culture. Growth was monitored by measuring the optical density at 600 nm (OD_{600}). After 6-7 h, the cultures reached an OD_{600} of 3 and were harvested by centrifugation (15 min, 8 000 $\times g$) and stored overnight at 4°C in a refrigerator. For the reaction, 250 μ l of 1 M potassium phosphate buffer (pH 7) and 250 μ l of 1M methyl 3-oxo-(2-thiophenyl)propanoate were added to 5 ml of the cell pellet and the whole was shaken in screw cap 13 ml glass tubes. 300 μ l of the reaction mixture were removed at regular intervals and extracted with 300 μ l of ethyl acetate or toluene. After the subsequent centrifugation (5 min, 5 000 $\times g$) for separating the phases, the organic phase was analysed by chiral gas chromatography. The results are recorded in Tab. 1.

Tabl 1

Reduction of methyl 3-oxo-(2-thiophenyl)propanoate using different yeast strains.

Example	Yeast strain	[c] of starting compound	Reaction time [h]	Product	Yield	ee (S)
1	NG 247	50 mM	24		75 %	> 97 %
2	Y278	50 mM	24		77 %	> 97 %

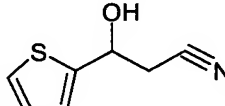
5

Example 3:

Reduction of 3-(2-thiophenyl)-3-oxopropano-1-nitrile using *Saccharomyces cereviseae* Y278.

- 10 The yeast cells were grown, and the reaction was carried out, as described in Examples 1 and 2. The result is recorded in Table 2.

Table 2

Example	Yeast strain	Starting compound conc.	Reaction time [h]	Product	Yield of product	ee (S)
3	Y278	20 mM	9		22 %	85 %

Examp l s 4 and 5:**Reduction of methyl 3-(2-thiophenyl)-3-oxopropanoate using
G o trichum candidum.**

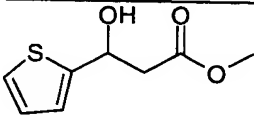
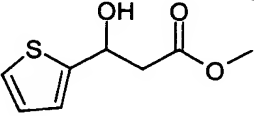
- 5 200 ml of YM medium were inoculated, in a 1-litre Erlenmeyer flask and as
the 1st preliminary culture, with the strain *Geotrichum candidum*
ATCC34614 and the flasks were incubated at 28°C for 18 h while being
shaken. As the 2nd preliminary culture, two 1-litre Erlenmeyer flasks, in
each case containing 200 ml of GC medium (KH₂PO₄, 11.18 g/l; K₂HPO₄,
10 3.12 g/l; glycerol, 30.0 g/l; yeast extract, 10.0 g/l; polypeptone, 5.0 g/l),
were in each case inoculated with 10 ml of the 1st preliminary culture and
likewise shaken at 28°C for 18 h.

- As the main culture, a 10 litre fermenter was loaded with 4.6 litres of GC
15 medium and inoculated with 400 ml of the 2nd preliminary culture. The
culture was grown at 28°C using an aeration rate of 10 l/min and a stirring
rate of 800 rpm. After 10 h, the fermenter was harvested. The cells were
sedimented by being centrifuged for 15 min at 6 000 \times g and were then
taken up in 100 mM potassium phosphate buffer (PP buffer), pH 6.4, and
20 stored at 4°C in a refrigerator.

- 1.8 g of glucose, 9 ml of 1M PP buffer (pH 7.3) and 71 μ l (final
concentration 20 mM) or 143 μ l (final concentration 40 mM) of methyl 3-
(2-thiophenyl)-3-oxopropanoate were added to 16 g of moist biomass and
25 the whole was stirred at 28°C in a 25 ml Schott bottle using a magnetic
stirrer. 300 μ l of the reaction mixture were removed at regular intervals
and extracted with 300 μ l of ethyl acetate or toluene and the organic
phase was analysed by gas chromatography. The results were recorded in
Table 3.

Tabl 3

Reduction of methyl 3-(2-thiophenyl)-3-oxo-propanoate with the strain *Geotrichum candidum* ATCC34614.

Example	Starting compound conc.	Reaction time [h]	Product	Yield of product	ee (S)
4	20 mM	10		71 %	>98 %
5	40 mM	10		72 %	> 98 %

5

Examples 6 to 12

Reduction of various β -ketoesters using *Saccharomyces cerevisiae*.

A preliminary culture of the strain *Saccharomyces cerevisiae* NG247 was grown overnight, at 28°C and while shaking, in 100 ml of YM medium in a 1-litre Erlenmeyer flask. As the main culture, three 1-litre Erlenmeyer flasks, which had each been loaded with 200 ml of YM medium, were in each case inoculated with 10 ml of the preliminary culture and shaken at 28°C. After 6 h, the cultures had reached an optical density of between 7 and 8 as measured at 600 nm (OD₆₀₀). The cells were harvested by centrifugation (15 min, 6 000 \square g) and resuspended in 100 mM PP buffer (pH 7) + 3% (w/v) glucose as a 10-fold concentrated cell suspension. 1M ethanolic solutions of the test substances were prepared. In the reaction mixtures, the cell suspension was in each case made to 20 mM with respect to the test substance and incubated at 30°C while being shaken. 300 μ l of the reaction mixture were withdrawn at regular intervals and extracted with 300 μ l of ethyl acetate or toluene and the organic phase was analysed by gas chromatography. The results are recorded in Tab. 4.

Table 4Enantioselective reduction of heterocyclic β -ketoesters.

Example	Starting compound	Starting compound conc.	Reaction time [h]	Product	Conversion %	ee %
6		20 mM	24 h		92 %	98 %
7		20 mM	24 h		50 %	87 %
8		20 mM	24 h		59 %	93 %
9		20 mM	24 h		92 %	81 %
10		20 mM	24 h		69 %	96 %
11		20 mM	24 h		76 %	96 %
12		20 mM	24 h		99 %	99 %

Example 13

Preparation of methyl 3-oxo-(2-thiophenyl)propanoate

510 ml of dimethyl carbonate and 1 500 ml of toluene were heated to
5 100°C in a 2L flask and a solution of 257 g of 2-acetylthiophene in 510 ml
of dimethyl carbonate was then added dropwise within the space of 4
hours. The methanol which was formed in the reaction was distilled off as
an azeotrope. 120 ml of conc. sulphuric acid were introduced, in 900 g of
ice, into a 4L flask and the cooled reaction mixture was added such that
10 40°C was not exceeded. The mixture was then stirred and the pH was
adjusted to pH 1. The phases were separated and the organic phase was
extracted three times by shaking with an aqueous solution of sodium
sulphate and then concentrated in vacuo. Vacuum distillation of the crude
product yielded 278 g of methyl 3-oxo-(2-thiophenyl)propanoate as a
15 transparent, slightly yellowish liquid (98% pure according to GC, 74% of
theory).

Example 14

Preparation of N-methyl-(3S)-3-hydroxy-3-(2-thienyl)propanamide

20

23 g of methyl (3S)-3-hydroxy-3-(2-thienyl)propanoate from experiments
described in the Examples 1 and [lacuna] were initially introduced, and
130 ml of a 2-molar methanolic solution of methylamine were added. This
mixture is stirred at 60°C for 4 h, cooled and then concentrated in vacuo.
25 24 g (purity 87%; 90% of theory) are obtained in this way. The crude
product can be used as such for the next step or else recrystallized from
methylene chloride and hexane. This yielded 18 g of N-methyl-(3S)-3-
hydroxy-3-(2-thienyl)propanamide (75% of theory) in the form of white
crystals.

30

Example 15**Preparation of (1S)-3-(methylamino)-1-(2-thienyl)-1-propanol**

350 ml of dry tetrahydrofuran are initially introduced together with 10 g of
5 lithium aluminium hydride and heated to reflux. At the same time, a start is
made in adding 17 g of N-methyl-(3S)-3-hydroxy-3-(2-thienyl)propanamide
from Example 14, dissolved in 150 g of tetrahydrofuran, dropwise. After
this dropwise addition is complete, the mixture is subsequently stirred
overnight under reflux. The mixture is then cooled down to room
10 temperature and 200 ml of water are carefully added dropwise. 135 ml of
a 10% solution of sodium hydroxide were then added dropwise and the
solution was filtered. The solvent was removed in vacuo. 370 ml of 1 N
sodium hydroxide solution were added to the crude solution and the whole
was extracted 3 times with in each case 370 ml of toluene. The organic
15 phases are combined and the volatile constituents are removed in vacuo,
thereby providing 76 g (84% purity, 70% of theory).

Example 16**Purification of (1S)-3-(methylamino)-1-(2-thienyl)-1-propanol**

20 15 g from Example 15 were dissolved in 150 ml of water at boiling heat,
after which 5 g of active charcoal were added and the mixture was
subsequently stirred under reflux for a further hour. The suspension was
filtered in the hot. The filtrate was extracted three times with in each case
25 100 ml of dichloromethane. The combined organic phases were
evaporated and the residue was dissolved, at boiling heat, in 50 ml of
cyclohexane; it was then crystallized, during cooling, using 600 ml of
petroleum ether. The crystals were filtered, washed with a little petroleum
ether and dried. This resulted in 12 g of (1S)-3-(methylamino)-1-(2-
30 thienyl)-1-propanol (98% purity, 93% yield).

Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention except as it may

5 be limited by the claims.